

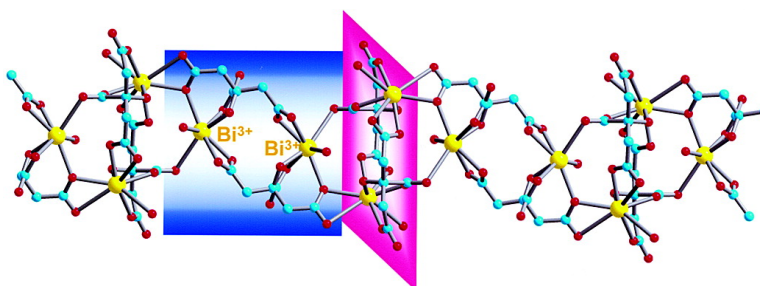
Communication

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Structure of Colloidal Bismuth Subcitrate (CBS) in Dilute HCl: Unique Assembly of Bismuth Citrate Dinuclear Units ($[\text{Bi}(\text{cit})_2\text{Bi}]^{2-}$)

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Bismuth compounds have long been associated with medicine and healthcare for the treatment of various diseases.¹ In combination with antibiotics, bismuth therapy has been recommended as a standard treatment for ulcers and *Helicobacter pylori* infection.^{2,3} Among the modern bismuth-containing pharmaceuticals, colloidal bismuth subcitrate (CBS, De-Nol and Lishudele) and ranitidine bismuth citrate (RBC, Pylorid) are the most widely used in many countries.³ Recently, a bismuth-based single-triple capsule containing CBS, metronidazole, and tetracycline has been approved for marketing in North America for the eradication of *Helicobacter pylori*.^{4,5} The mechanism of action of CBS possibly involves the formation of bismuth citrate “polymeric coating” on ulcer craters to prevent the erosion by gastric acid.^{1b,2} Indeed, tiny crystalline species have been observed in ulcer craters of animal models and patients after administration with colloidal bismuth subcitrate.^{6,7}

Efforts have been made to elucidate the structure of CBS and RBC, with nine bismuth citrate complexes having been crystallized and characterized so far. However, eight of these were crystallized at neutral pH values.^{8–13} It is known that speciation of Bi^{3+} (and other metal) citrate complexes is pH dependent.¹⁴ To understand the pharmacokinetics and dynamics of bismuth citrate drugs in the stomach, we have attempted to unveil the three-dimensional structure of CBS under acidic conditions ($\text{pH} \approx 3$). Upon addition of dilute HCl to colloidal bismuth subcitrate, a white precipitate formed. The bismuth concentration in the filtrate was found to decrease dramatically from over 70 mg/mL at pH 6.7 to only 1 mg/mL at pH 3 (Figure S1). Upon observation under microscope, it was revealed that precipitate **1** that was isolated at pH 3 consisted of tiny crystals (Figure S2). On standing at room temperature for several days, colorless crystals of $\text{K}(\text{NH}_4)[\text{Bi}_2(\text{cit})_2(\text{H}_2\text{O})_2] \cdot 4\text{H}_2\text{O}$, **1**, suitable for X-ray analysis, formed in the filtrate ($\text{pH} \approx 3$).^{15,16} In contrast to structures obtained previously for bismuth citrate ($\text{Bi}:\text{cit} = 1:1$) and other metal citrate complexes, X-ray crystallography revealed the presence of three types of bismuth citrate dinuclear unit $[\text{Bi}(\text{cit})_2\text{Bi}]^{2-}$ in **1** with $\text{Bi} \cdots \text{Bi}$ separation from 5.735 to 6.082 Å (Figure 1). In these dimers, each Bi^{3+} is coordinated to three oxygens from one tetraanionic citrate (cit^{4-}) in a tridentate mode and a doubly bridged terminal carboxylate group from another citrate. The coordination of each bismuth in the dimer **I** is complemented by a monodentate oxygen from a citrate belonging to the adjacent dimer ($\text{Bi}-\text{O}$ 2.788(9) Å) and one water molecule ($\text{Bi}-\text{O}$, 2.445(15) Å, Figures 1 and 2). Dimers **II** and **III** are structurally very similar to one another, with the coordinations of Bi^{3+} complemented by a bidentate carboxylate from a third citrate and an oxygen either from a water molecule (dimer **II**) or from a citrate (dimer **III**). The two $[\text{Bi}(\text{cit})]^-$ units from the asymmetric part are paired by a C_2 axis in dimer **I**, which is similar to those

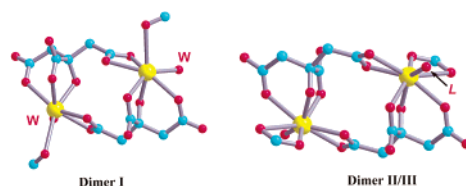


Figure 1. Basic dimeric units $[\text{Bi}(\text{cit})_2\text{Bi}]^{2-}$ found in **1** with a C_2 symmetry (dimer **I**) and an inversion center (dimer **II/III**). In dimer **I**, “W” represents a water molecule, while in dimer **II/III**, the “L” represents either an oxygen from a water molecule (dimer **II**) or a citrate carboxylate (dimer **III**). Color code: C, cyan; O, red; Bi, yellow.

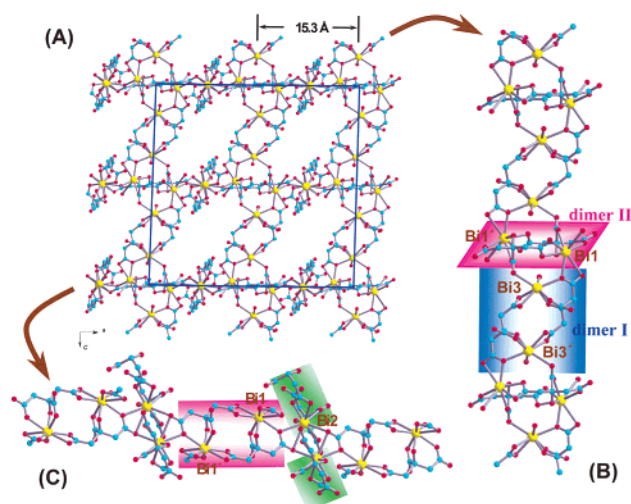


Figure 2. Projection of the X-ray structure of complex **1** down the b axis (A) and the polyanionic chain of $[\text{Bi}(\text{cit})_2\text{Bi}]^{2-}$ along the c axis formed by the aggregation of dimers **I** and **II** (B), and along the a axis by the aggregation of dimers **II** and **III** (C). All potassium and ammonium ions, hydrogen atoms, and free lattice water molecules are omitted for clarity.

observed previously.^{8–11,13} However, this is the first time that a centrosymmetric structure, as found in dimers **II/III**, has been observed for a bismuth citrate structure, Figure 1. The coordination numbers of Bi^{3+} in **I** and **II/III** are seven and eight, respectively.

The unique spatial assembly of these dimers leads to the formation of two-dimensional sheets and three-dimensional anionic polymers (Figures 2 and S3). In the projection of the ac plane along the c axis, dimers **I** ($\text{Bi}3-\text{Bi}3'$) and **II** ($\text{Bi}1-\text{Bi}1'$) aggregate linearly to form an infinite polyanion. Distinct from other bismuth citrate (and other metal citrate) complexes, dimer **II** ($\text{Bi}1-\text{Bi}1'$) is inserted vertically into adjacent building units (dimer **I**) (Figure 2B). The terminal carboxylate oxygens, with one singly coordinated to $\text{Bi}3$ in dimer **I**, are used to form a link to dimer **II** in a bidentate mode ($\text{Bi}-\text{O}$ 2.510(9) and 2.955(10) Å). One central citrate carboxylate oxygen in dimer **II**, which does not participate in the tridentate chelation, is linked to one bismuth ($\text{Bi}3$) in dimer **I** ($\text{Bi}-\text{O}$ 2.788-

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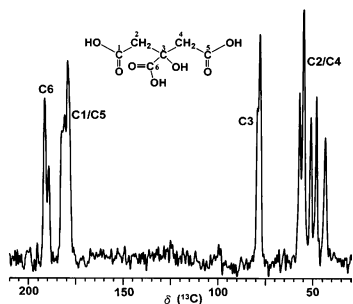


Figure 3. Solid-state CP/MAS ^{13}C NMR spectrum (spinning speed = 8 kHz, contact time = 5 ms) of **1** showing more than 12 carbon signals, indicative of the presence of three types of dimers. The assignments together with the structure of citric acid are also shown.

(9) Å). The aggregation formed by dimers **I** and **II**, through strong covalent bonds, results in a “tetrameric unit” and subsequently a “linear chain” (parallel to the c axis of the unit cell). Interestingly, the adjacent dimers **I** with half of their dimeric units ($[\text{Bi}(\text{cit})]^-$) forming a structure with C_2 symmetry are in an inversion center, while dimers **II** with half of their units being a centrosymmetric structure are in a C_2 symmetry. The paralleled linear chains (15.3 Å apart) are further cross-linked by primary coordination of citrate oxygens from dimers **II** to bismuth from an orthogonal direction.

In contrast to the assembly between **I** and **II** along the c axis, dimer **II** is linked by two bismuth ions from two different dimers (dimer **III**) via citrate bridging, as may be seen in Figures 2C and S3 (in the a,b plane of the polymer). The terminal carboxylate oxygen with one singly coordinated to Bi1 in dimer **II** (Bi–O 2.515(8) Å) is used to link one Bi^{3+} from dimer **III** (Bi–O 2.520(8) Å), while the other oxygen from this carboxylate which does not participate in the tridentate chelation bridges two Bi^{3+} from different dimers **III** (Bi–O 2.708(9) and 2.848(9) Å) from the b axis. The two halves of the dimeric unit are linked by a C_2 axis such that the central four-membered Bi_2O_2 ring is constrained to be planar with a O–Bi–O angle of 88.7°. Such an aggregation also leads to the formation of a linear anionic chain (Figures 2C and S3). Dimer **III** also assembles into a polyanion along the b axis (Figure S3). Interestingly, the carboxylate oxygens bridging the two adjacent dimers **III** are from a third citrate. There is actually no direct bonding between two adjacent dimers **III** except a weak interaction (Bi–O 3.242 Å).

Cross-linking between linear polymers from different directions results in the formation of two-dimensional network (sheets) and 3D structures, making a large mesh with channels (Figure 2A). The requisite number of potassium and ammonium ions necessary for charge balance are embedded within the meshes and channels, forming a contact with both citrate and water oxygens (Supporting Information). The potassium and ammonium ions are structurally interchangeable. In addition, a number of free water molecules are also situated within the meshes and channels, forming extensive hydrogen bonds with citrates.

To investigate the structure of different dimers in **1** and allow comparison of **1** with other known bismuth citrate complexes, the solid-state ^{13}C CP/MAS NMR spectrum of **1** was recorded, Figure 3. On the basis of our previous analysis of similar complexes,¹³ the lowest-field peaks at 191.4 and 189.6 ppm, and several overlapped peaks at around 180 ppm, can be assigned to the central (C6) and terminal carboxylates (C1/C5), respectively. Although we cannot rationalize the number of carbons based on the intensity of a peak, it is still possible to compare the number of carbons semiquantitatively for the same type of carbon. The intensity of the peak at 191.4 ppm is almost 2-fold higher than the one at 189.6 ppm, suggesting that there are two overlapping carbon signals at

191.4 ppm. The two peaks at 79.4 and 78.2 ppm can be assigned to the central carbon (C3), with the intensity of the latter being 2-fold higher than that of the former. The five peaks at 57.1, 55.1, 51.3, 48.4, and 43.7 ppm can be assigned to C2 and C4 which are directly bonded to protons (Figure 1). The intensity of the peak at 55.1 ppm is almost 2 times greater than that of others in this region, again indicative of two overlapping carbons. In contrast, only one signal (C1–C6) was observed for each carbon in $\text{Na}_2[\text{Bi}_2(\text{cit})_2] \cdot 7\text{H}_2\text{O}$.¹³ This suggests that there are three types of citrate anions in complex **1**, which is in full agreement with the X-ray crystal structure. Of these three citrate anions, two are in very similar environments, corresponding to citrates in dimers **II/III**.

In summary, we have shown the first example of three types of bismuth citrate dinuclear units $[\text{Bi}(\text{cit})_2\text{Bi}]^{2-}$ which function as building blocks, assembling into a three-dimensional polymer. CBS may rearrange from colloidal particles such as $[\text{Bi}_6\text{O}_4(\text{cit})_4]^{6-}$ and $[\text{Bi}_{12}\text{O}_8(\text{cit})_8]^{12-}$ at neutral pH value,¹² to sheets and 3D polymers under acidic conditions (e.g., in the stomach) due to rapid ligand exchange. Solid-state ^{13}C NMR confirmed the presence of three types of citrate in polymer **1**. Because the complex has a significant resistance to acid (HCl), it can be regarded as the potential “active species” of the antiulcer drug CBS in the stomach and is thus a possible candidate for the tiny crystals (“coating”) found on the ulcer craters.⁶

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Supporting Information Available: Experimental procedures, three figures, and one table (PDF and CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (15) Tiny colorless crystals of dimensions $0.3 \times 0.2 \times 0.1 \text{ mm}^3$ were obtained from a filtrate of CBS after addition of dilute HCl at pH 3. Elemental analysis of **1** (calc): C, 15.11 (15.02); H, 2.65 (2.52); N, 1.42 (1.46).
- (16) Crystal data for **1**: $(\text{C}_{12}\text{H}_{24}\text{NO}_{20}\text{KBi}_2)_{3/2}$, monoclinic $C2/c$, $a = 28.961(6)$, $b = 9.6050(19)$, $c = 28.086(6)$ Å, $\alpha = 90^\circ$, $\beta = 91.17(3)^\circ$, $\gamma = 90^\circ$, $V = 7811(3)$ Å³, $Z = 8$, $D_c = 2.399 \text{ g/cm}^3$, $\mu(\text{Mo K}\alpha) = 13.689 \text{ mm}^{-1}$, $T = 301(2)$ K, $\lambda = 0.71073$ Å, 23 402 reflections collected, 8789 independent reflections ($R_{\text{int}} = 0.1103$), $R_1 = 0.0603$, $wR_2 = 0.1652$ [$I > 2\sigma(I)$]. The structure was solved by direct method (SHELXS-97) and refined against all independent F^2 data (SHELXS-97).

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